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Convenient synthesis of trifluoromethylated 2-pyrrolidone and 2-pyrrolone derivatives

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ABSTRACT

The reaction of a set of enamines with methyl trifluoropyruvate and its imine was investigated. As a result, a simple procedure for synthesis of trifluoromethylated 2-pyrrolidone and 2-pyrrolone derivatives has been developed.

1. Introduction

Five-membered nitrogen heterocycles are widely present in natural compounds and are structural part of various pharmacologically active compounds. Among these heterocycles, pyrrolidone, pyrrolone, pyrrolidine play a special role because they are a part of various alkaloids [1–4]. Although these compounds are in great demand, general methods for their synthesis are absent. There a few many step approaches often using hardly accessible compounds [5,6].

Concerning trifluoromethylated analogues of these compounds there are only few works [7]. In some cases [7a,7b], reaction conditions are quite harsh, for example 90–100 °C in DMF during 5 h. As introduction of fluorine atoms into hit and lead compounds is an effective and established tool to fine tune various physical and biological parameters need for fluorinated analogues of these heterocyles is high [8,9]. One of the methods for introducing trifluoromethyl group is based on use of esters of trifluoropyruvic acid. Thus, this method was successfully used for the synthesis of various fluoro-containing aromatic and heteroaromatic compounds [10]. Previously we have shown that methyl trifluoropyruvate **1** and its imine **2** easily react with tertiary "push–pull" enamines giving α-hydroxy(or α-amino)-α-trifluoromethylated compounds [11]. It should be noted that α-hydroxy-α-trifluoromethyl amide derivatives are frequently used in pharmaceuticals [12]. Using this approach we have developed a simple and effective method for synthesizing trifluoromethylated 2-pyrrolidone and 2-pyrrolone derivatives starting from readily available methyl trifluoropyruvate and enamines.

2. Results and discussion

For our purposes we used methyl trifluoropyruvate (MeTFP) **1a** (X = O) and N-substituted imine of MeTFP **1b** (X = NCO_2Et) and a set of primary and secondary enamines **2** having various electron withdrawing groups at the β-position. We have shown that mainly the reaction proceeds under mild conditions in dry benzene in few hours without a catalyst, in some cases the reaction can be run neat (Table 1). It appeared that MeTFP **1a** and imine **1b** in the reaction with enamines **2–4** gave various products (Scheme 1). Thus, for example, enamine **2** (EWG = CN) reacts with **1(a,b)** giving α-hydroxy(or α-amino)-α-trifluoromethylated 2-pyrrolone derivatives **5** in good preparative yields. The reaction comes to completion at room temperature (for imine of MeTFP **1b** at 50 °C) in 1–2 h. The reaction proceeds via tandem aldol condensation–cyclization pathway through participation of the β-carbon atom and the amino group of the enamines. The reaction runs neat. In this case an equimolar mixture of the reagents is kept at room temperature for 2 h (for imine of MeTFP **1b** at 50 °C during 3 h) followed by treatment with chloroform resulting in α-hydroxy(or

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Table 1
Yields and methods applied for the synthesis of compounds **5–7**.

Entry	EWG	R	R′	X	Method	Yield (%)
5a	[1,0]CN	H	–	O	A	78
					B	86
5b		H	–	NCO_2Et	A	73
5c	CO_2Et	H	–	NCO_2Et	A	89
					B	71
5d		Me	–	NCO_2Et	A	91
					B	88
6		H	H	O	B	98
7a		H	H		A	96
					B	98
7b		Me	H		B	95
7c		Me	Et		B	89
7d	COMe	H	H			83
7e		Me	H		B	85

α-amino)-α-trifluoromethylated 2-pyrrolone derivatives **5** in good preparative yields. Under these reaction conditions the reaction can be scaled up so that 2-pyrrolone derivatives **5** can be prepared in multigrams.

Unlike enamines **2**, enamines **3** (EWG = CO_2Et) react with MeTFP **1a** with participation of the methyl group of the enamines affording functionalized enamines **6**. The reaction proceeds in equimolar ratio of the reagents at room temperature in benzene in quantitative yield. In NMR ^{19}F spectrum one signal of trifluoromethyl group at −80 ppm typical for the trifluoromethyl group attached to sp^3-hybridized carbon atom.

At the same time ^1H NMR spectrum of the compound **6** exhibits two proton singlet instead of the expected AB-system of the methylene group due to the presence of chiral center. As the compound **6** is not a crystalline we have failed to make an X-rays analysis. Mass-spectrum of the compound **6** has a molecular peak of high intensity (MS 70 eV EI: *m*/*z* (%) = 385 (22) [M^+]).

β′-Functionalized enamine **6** appeared to be stable in solid state, but it spontaneously cyclizes into в 2-pyrrolidone derivative **7a** in solution. Cyclization comes to completion in 1 h in aqueous methanol at room temperature and almost immediately upon heating. ^1H NMR spectrum of the product has AB-system of methylene group, unlike compound **6.** ^{13}C NMR spectra exhibit signal of CH_2-carbon atom ∼35 ppm that was proved by APT experiment and signal of CH carbon atom at ∼98 ppm. Position of double bond at compounds **7** was proved by X-rays analysis. It has been found that its position depends on nature of a substituent at nitrogen atom. Thus, compound **7a** (R = H) has (*Z*) configuration due to intramolecular hydrogen bonding between amide group and oxygen atom of the carbonyl group (Fig. 1). As hydrogen bonding is impossible for compound **7b** (R = Me), it acquires (E) configuration (Fig. 2).

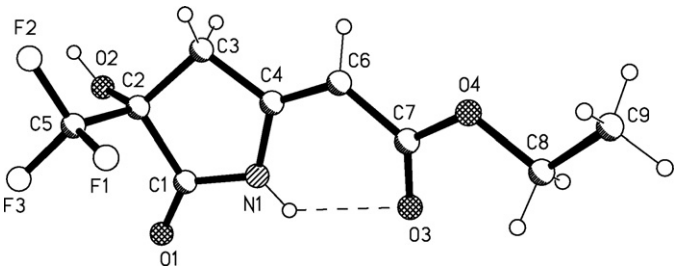


Fig. 1. A perspective view and labeling scheme for the molecule **7a**.

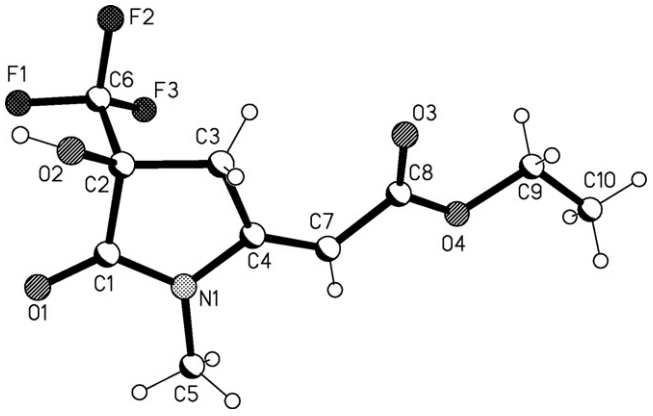
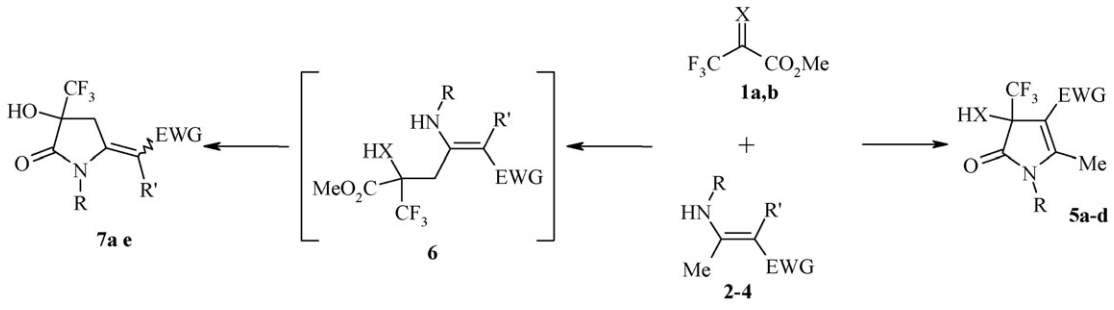


Fig. 2. A perspective view and labeling scheme for the molecule **7b**.

The reaction between enamines **3** with imine of MeTFP **1b** proceeds with participation of the β-carbon atom and the amino group of the enamines. As a result the sole products of the reaction are 2-pyrrolone derivatives **5(c,d)**.

Contrary to enaminoesters **3**, enaminones **4** react with MeTFP **1a** directly affording cyclic products **7**. Since acyl group is more acceptor group compared to ester group it can be accounted for higher activity of enamines **4** towards MeTFP. Spectral data testify unambiguously for participation of the methyl group of the enamines. Earlier similar reactions of enamines with strong electrophiles have been shown to proceed [11,13] by ene type mechanism. Formation of compounds **5** could not be explained by this mechanism and most probably proceeds by an electrophilic substitution mechanism typical for enamines [14].

In conclusion, a convenient method for synthesis of trifluoromethylated 2-pyrorlidine and 2-pyrrolone derivatives has been elaborated. Readily available starting materials and simple synthetic procedure make this method very attractive and convenient for the synthesis of α-hydroxy-α-trifluoromethyl



Scheme 1. Synthesis of compounds **5–7**.

amide derivatives which are useful building blocks for organic and medicinal chemistry.

3. Experimental

3.1. General

All solvents were purified and dried by standard methods. ^{1}H NMR spectra were recorded on a Varian VXR-300 spectrometer and ^{13}C NMR spectra were recorded on a Varian Mercury-400 spectrometer. ^{1}H and ^{13}C NMR spectra were measured at 300 and 100 MHz, respectively with TMS as an internal standard. Mass spectra were obtained on a MX-1321 instrument (EI, 70 eV) by direct inlet or on VG 70-70EQ, VG ANALYTICAL (FAB). Microanalyses were performed in the Microanalytical Laboratory of the Institute of Organic Chemistry National Academy of Sciences of Ukraine. Starting imine of MeTFP **1b** was prepared according to the literature [15].

3.2. General procedure for the reaction of enamines 2–4 with 1

Method A: To a solution of the corresponding enamine (0.024 mol) in benzene (30 ml) was added **1** (0.024 mol). The reaction mixture was left at rt for 1 h in case of MeTFP **1a** or was heated at 50 °C during 3 h for imine of MeTFP **1b**. The solvent was evaporated in vacuo and the residue was crystallized from an appropriated solvent.

Method B: A mixture of the enamine (0.024 mol) and **1** (0.024 mol) was left at rt for 2 h in case of MeTFP **1a** or was heated on oil bath at 50 °C during 3 h for imine of MeTFP **1b**. The residue was washed with hexane and was crystallized from an appropriated solvent.

3.2.1. 4-Hydroxy-2-methyl-5-oxo-4-(trifluoromethyl)-4,5-dihydro-1H-pyrrole-3-carbonitrile (5a)

Method A and B was applied. The residue was crystallized from chloroform. White solid. Mp = 170 °C. ^{1}H NMR (DMSO-d_6): δ = 2.2 (3H, s, CH_3), 7.97 (1H, br s, OH), 8.32 (1H, s, NH) ^{13}C NMR (DMSO-d_6): δ = 14.0, 76.6 ($^2J_{C-F}$ = 31 Hz, CCF_3), 84.5, 113.9, 123.3 ($^1J_{C-F}$ = 285 Hz, CF_3), 163.6, 171.8. ^{19}F NMR (DMSO-d_6): δ = −77.6. MS (EI): m/z (%) = 206 (35) [M$^+$], 137 (54), 109 (38), 68 (61), 42 (100). Anal. Calcd. for $C_7H_5F_3N_2O_2$: C 40.79; H 2.45; N 13.59. Found: C 40.77; H 2.43; N 13.58.

3.2.2. Ethyl [4-cyano-5-methyl-2-oxo-3-(trifluoromethyl)-2,3-dihydro-1H-pyrrol-3-yl]carbamate (5b)

Method A was applied. The product was precipitated from the reaction mixture, filtered and washed with hexane. White solid. Mp = 167 °C. ^{1}H NMR (DMSO-d_6): δ = 1.18 (3H, t, $^3J_{H-H}$ = 7.2 Hz, CH_3), 2.2 (3H, s, CH_3), 4.05 (2H, q, $^3J_{H-H}$ = 7.2 Hz, CH_2), 9.2 (1H, s, NH), 11.3 (1H, br s, NH). ^{13}C NMR (DMSO-d_6): δ = 14.3, 14.6, 61.6, 65.7 ($^2J_{C-F}$ = 29 Hz, CCF_3), 82.7, 114.3, 123.6 ($^1J_{C-F}$ = 284 Hz, CF_3), 154.8, 163.7, 170.4. ^{19}F NMR (DMSO-d_6): δ = −75.6. MS (EI): m/z (%) = 277 (22) [M$^+$], 208 (16), 136 (100), 67 (11), 42 (45). Anal. Calcd. for $C_{10}H_{10}F_3N_3O_3$: C 43.33; H 3.64; N 15.16. Found: C 43.35; H 3.66; N 15.15.

3.2.3. Ethyl 4-[(ethoxycarbonyl)amino]-2-methyl-5-oxo-4-(trifluoromethyl)-4,5-dihydro-1H-pyrrole-3-carboxylate (5c)

Methods A and B were applied. The residue was tritruated with diethyl ether. White solid. Mp = 158 °C. ^{1}H NMR ($CDCl_3$): δ = 1.19 (t, $^3J_{H-H}$ = 7.2 Hz, 3H, CH_3), 1.28 (t, $^3J_{H-H}$ = 7.2 Hz, 3 H, CH_3), 2.47 (3H, CH_3), 4.05 (q, 2H, $^3J_{H-H}$ = 7.2 Hz, OCH_2), 4.18 (q, 2H, $^3J_{H-H}$ = 7.2 Hz, OCH_2), 7.45 (1H, NH), 9.91 (1H, NH). ^{13}C NMR ($CDCl_3$): δ = 14.5, 14.8, 18.6, 59.5, 61.0, 65.8 ($^2J_{C-F}$ = 28.8 Hz, CCF_3), 101.1, 123.6 ($^1J_{C-F}$ = 283.3 Hz, CF_3), 154.9, 160.1, 162.6, 171.7. ^{19}F NMR ($CDCl_3$): δ = −74.5. MS (EI): m/z (%) = 324 (18) [M$^+$], 255 (43), 183 (21), 137 (100). Anal. Calcd. for $C_{12}H_{15}F_3N_2O_5$: C 44.45; H 4.66; N 8.64. Found: C 44.47; H 4.65; N 8.63.

3.2.4. Ethyl 4-[(ethoxycarbonyl)amino]-1,2-dimethyl-5-oxo-4-(trifluoromethyl)-4,5-dihydro-1H-pyrrole-3-carboxylate (5d)

Methods A and B were applied. The residue was subjected to silica gel column chromatography using ethyl acetate:hexane = 1:1 as eluent (Rf = 0.6). Pale yellow solid. Mp = 87 °C. ^{1}H NMR ($CDCl_3$): δ = 1.21 (t, $^3J_{H-H}$ = 7.2 Hz, 3 H, CH_3), 1.28 (t, $^3J_{H-H}$ = 7.2 Hz, 3 H, CH_3), 2.58 (3H, CH_3), 3.16 (3H, CH_3), 4.09 (2H, CH_2), 4.21 (q, 2H, $^3J_{H-H}$ = 7.2 Hz, OCH_2), 5.62 (1H, NH). ^{13}C NMR ($CDCl_3$): δ = 14.1, 14.3, 20.6, 26.9, 59.9, 61.9, 64.7 ($^2J_{C-F}$ = 28.1 Hz, CCF_3), 101.6, 122.1 ($^1J_{C-F}$ = 283.6 Hz, CF_3), 154.6, 160.7, 162.6, 169.5. ^{19}F NMR ($CDCl_3$): δ = −76.3. MS (EI): m/z (%) = 338 (22) [M$^+$], 269 (51), 197 (24), 136 (100). Anal. Calcd. for $C_{13}H_{17}F_3N_2O_5$: C 46.16; H 5.07; N 8.28. Found: C 46.17; H 5.05; N 8.29.

3.2.5. 1-Ethyl 6-methyl 3-amino-5-hydroxy-5-(trifluoromethyl)-2-hexendicarboxylate (6)

Method B was applied. Products are analytically pure. Yellow oil. ^{1}H NMR ($CDCl_3$): δ = 1.24 (t, $^3J_{H-H}$ = 7.2 Hz, 3 H, CH_3), 2.72 (2H), 3.92 (3H, CH_3), 4.1 (2H, CH_2), 4.28 (1H), 4.48 (1H). ^{13}C NMR ($CDCl_3$): δ = 14.4, 37.7, 54.4, 58.9, 77.8 ($^2J_{C-F}$ = 30 Hz, CCF_3), 86.4, 122.8 ($^1J_{C-F}$ = 285 Hz, CF_3), 155.7, 168.6, 169.9. ^{19}F NMR ($CDCl_3$): δ = −80.0. MS (EI): m/z (%) = 285 (20) [M$^+$], 240 (19), 213 (37), 180 (100). Anal. Calcd. for $C_{10}H_{14}F_3NO_5$: C 42.11; H 4.95; N 4.91. Found: C 42.09; H 4.93; N 4.89.

3.2.6. Ethyl [4-hydroxy-5-oxo-4-(trifluoromethyl)pyrrolidin-2-ylidene]acetate (7a)

Methods A and B were applied. The residue was crystallized from aqueous methanol. White solid. Mp = 68 °C. (*Note*: The compound can be obtained by heating of **6** in aqueous methanol during 10 min. After cooling the precipitate of **7a** are formed). ^{1}H NMR ($CDCl_3$): δ = 1.27 (t, $^3J_{H-H}$ = 7.2 Hz, 3 H, CH_3), 3.11 and 3.28 (AB-system, $^2J_{H-H}$ = 18 Hz, 2H), 4.19 (q, 2H, $^3J_{H-H}$ = 7.2 Hz, OCH_2), 5.14 (2H), 10.4 (1H). ^{13}C NMR (DMSO-d_6): δ = 14.2, 47.1, 59.5, 73.2 ($^2J_{C-F}$ = 30 Hz, CCF_3), 91.9, 124.1 ($^1J_{C-F}$ = 285 Hz, CF_3), 150.8, 165.9, 171.1. ^{19}F NMR ($CDCl_3$): δ = −81.8. MS (EI): m/z (%) = 253 (70) [M$^+$], 208 (77), 184 (35), 181 (35), 180 (33), 179 (30), 138 (64), 85 (60), 69 (31), 68 (100). Anal. Calcd. for $C_9H_{10}F_3NO_4$: C 42.70; H 3.98; N 5.53. Found: C 42.71; H 4.01; N 5.55.

3.2.7. Ethyl [4-hydroxy-1-methyl-5-oxo-4-(trifluoromethyl)pyrrolidin-2-ylidene]acetate (7b)

Method B was applied. The residue was crystallized from aqueous methanol. White solid. Mp = 78–80 °C. ^{1}H NMR ($CDCl_3$): δ = 1.28 (t, $^3J_{H-H}$ = 7.2 Hz, 3H, CH_3), 3.11 (3H, CH_3), 3.29 and 3.81 (AB-system, $^2J_{H-H}$ = 19.2 Hz, 2H), 4.21 (q, 2H, $^3J_{H-H}$ = 7.2 Hz, OCH_2), 5.38 (1H, CH). ^{13}C NMR (DMSO-d_6): δ = 14.2, 27.4, 34.6, 60.3, 74.1 ($^2J_{C-F}$ = 31 Hz, CCF_3), 95.1, 123.5 ($^1J_{C-F}$ = 283 Hz, CF_3), 153.3, 166.6, 170.8. ^{19}F NMR ($CDCl_3$): δ = −81.7. Anal. Calcd. for $C_{10}H_{12}F_3NO_4$: C 44.95; H 4.53; N 5.24. Found: C 44.96; H 4.52; N 5.23.

3.2.8. Ethyl 2-[4-hydroxy-1-methyl-5-oxo-4-(trifluoromethyl)pyrrolidin-2-ylidene]butanoate (7c)

Method B was applied. The residue was crystallized from aqueous methanol. White solid. Mp = 88 °C. ^{1}H NMR ($CDCl_3$): δ = 1.08 (t, $^3J_{H-H}$ = 7.2 Hz, 3H, CH_3), 1.31 (t, $^3J_{H-H}$ = 7.2 Hz, 3H, CH_3), 2.57 (2H, m, CH_2), 3.36 (3H, CH_3), 3.21 and 3.66 (AB-system, $^2J_{H-H}$ = 18 Hz, 2H), 4.21 (2H, m OCH_2). ^{13}C NMR ($CDCl_3$): δ = 14.2, 15.1, 20.7, 32.0, 37.6, 60.7, 74.2 ($^2J_{C-F}$ = 31.4 Hz, CCF_3), 112.9, 123.4 ($^1J_{C-F}$ = 285.4 Hz, CF_3), 145.5, 168.1, 172.1. ^{19}F NMR ($CDCl_3$): δ = −81.5. Anal. Calcd. for $C_{12}H_{16}F_3NO_4$: C 48.82; H 5.46; N 4.74. Found: C 48.81; H 5.46; N 4.73.

3.2.9. 3-Hydroxy-5-(2-oxopropylidene)-3-(trifluoromethyl)-2-pyrrolidone (7d)

Method A was applied. The residue was crystallized from cold chloroform. Mp = 120 °C ^{1}H NMR ($CDCl_3$): δ = 2.25 (3H, CH_3), 3.03 and 3.24 (AB-system, $^2J_{H-H}$ = 18.3 Hz, 2H), 4.45 (1H, OH), 5.62 (1H, CH), 11.03 (1H, NH). ^{13}C NMR (DMSO-d_6): δ = 29.1, 40.3, 74.9 ($^2J_{C-F}$ = 28 Hz, CCF_3), 101.6, 123.4 ($^1J_{C-F}$ = 285.5 Hz, CF_3), 149.1, 168.3, 196.4. ^{19}F NMR ($CDCl_3$): δ = −81.6. MS (EI): m/z (%) = 223 (38) [M^+], 208 (37), 180 (32), 154 (28), 83 (26), 68 (35), 43 (100). Anal. Calcd. for $C_8H_8F_3NO_3$: C 43.06; H 3.61; N 6.28. Found: C 43.07; H 3.58; N 6.32.

3.2.10. 3-Hydroxy-1-methyl-5-(2-oxopropylidene)-3-(trifluoromethyl)-2-pyrrolidone (7e)

Method B was applied. The residue was crystallized from diethyl ether. Mp = 136 °C. ^{1}H NMR ($CDCl_3$): δ = 2.27 (3H, CH_3), 3.12 (3H, CH_3), 3.33 and 3.79 (AB-system, $^2J_{H-H}$ = 19.8 Hz, 2H), 4.53 (1H, OH), 5.81 (1H, CH). ^{13}C NMR (DMSO-d_6): δ = 28.1, 31.8, 36.3, 73.9 ($^2J_{C-F}$ = 30 Hz, CCF_3), 102.5, 124.5 ($^1J_{C-F}$ = 281 Hz, CF_3), 152.6, 170.5, 197.0. ^{19}F NMR ($CDCl_3$): δ = −81.3. MS (EI): m/z (%) = 237 (40) [M^+], 222 (100), 194 (24), 168 (27), 82 (31), 43 (37). Anal. Calcd. for $C_9H_{10}F_3NO_3$: C 45.58; H 4.25; N 5.91. Found: C 45.61; H 4.25; N 5.92.

3.3. X-ray crystallography

Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC-743356 (**7a**) and CCDC-743343 (**7b**) and can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (internat.) +44-1223/336-033; e-mail: deposit@ccdc.cam.ac.uk).

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